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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,055	09/05/2003	Debbie Yaver	10322.200-US	8946
25907	7590	04/22/2008	EXAMINER	
NOVOZYMES, INC. 1445 DREW AVE DAVIS, CA 95616			HINES, JANA A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/656,055	Applicant(s) YAYER ET AL.	
	Examiner JaNa Hines	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 February 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 11, 36, 42, 43, 82-88 and 90-93 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 11, 36, 42, 43, 82-88 and 90-93 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>2/5/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Amendment Entry

1. The amendment filed on February 5, 2008 has been entered. Claims 1, 36, 82-87 and 90-93 have been amended. Claims 2-10, 12-35, 37-41, 44-81 and 89 are cancelled. Claims 1, 11, 36, 42-43, 82-88 and 90-93 are under consideration in this office action.

Withdrawal of Rejections

2. The following rejections have been withdrawn in view of applicants' amendments and arguments:

- a) The new matter rejection of claims 82-87 under 35 U.S.C. 112, first paragraph;
and
- b) The rejection of claims 1, 11, 36, 42, 43, 82-87 and 90-93 under 35 U.S.C. 112, second paragraph.

Previous Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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3. Claims 1, 11, 36, 42-43, 82-88 and 90-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al., (PNAS, 1999. Vol. 96(22): 12833-12838) in view of Cao et al., (Mol. Microbio. 2002. Vol. 45(5): 1267-1276).

The claims are drawn to a method for determining the mode of action of an antimicrobial compound, comprising: a) detecting hybridization complexes formed by contacting at least one nucleic acid sample, obtained by culturing *Bacillus subtilis* cells in the presence of at least one subinhibitory amount of an antimicrobial compound having an unknown mode of action, with a plurality of nucleic acid sequence corresponding to genes of the *Bacillus subtilis* cells, wherein the plurality of nucleic acid sequences is contained on a substrate, wherein the presence, absence or change in the amount of the hybridization complexes detected, compared with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode action, is indicative of the similarity of the mode of actions of the antimicrobial compound and the standard compound; and b) assigning a mode of action for the antimicrobial compound based on the similarity of values assigned to the hybridization complexes detected in (a) based on the hybridization complexes formed from the second nucleic acid sample. The dependant claims are drawn to action of the antimicrobial compound and the source of the plurality of nucleic acids.

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Wilson et al., teach exploring drug-induced alterations in gene expression by microarray hybridization. Wilson et al., teach drugs and compounds selectively induce changes in the transcription of genes, and the resulting gene expression profile would serve as a signature of the inhibitor used especially in cases of inhibitors whose modes of action were unknown (page 12,833). Wilson et al., teach the ability for pathway characterization is available because complete genome sequences are known and microarrays containing representatives of each of the genes are known (page 12,833). Wilson et al., teach the preparation of DNA microarrays which contains genomic sequences and fragments on a substrate (page 12,834). Wilson et al., teach culturing, growth and drug treatment of the bacterial strains with the drug (page 12,834). Wilson et al., teach microarray hybridization where the DNA was applied to the array in a hybridization mixture which allowed hybridization to occur (page 12,835). Wilson et al., teach the detection of hybridization complexes formed by contacting at least one nucleic acid with a plurality of nucleic acid sequences corresponding to genes of the bacterial cells. Wilson et al., teach the microarray hybridization provides a characteristic signature for the cellular processes that are affected by the compound (page 12,838). Wilson et al., teach the drug response profiles were distinct from the profiles obtained from bacteria exposed in a similar manner to a variety of different compounds (page 12,838).

Wilson et al, teach a generated response to isoniazid (INH), thus the antimicrobial compound is a member of the class of compounds which interferes with the cell membrane. Wilson et al., teach that this system provides the framework for

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interpreting the transcriptional responses that we would detect by the microarray hybridization and allow for comparison with published results of genes and proteins that are known to be INH induced (page 12,833). Wilson et al., teach the comparison with hybridized complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from bacterial cells cultured in the absence or presence of a standard compound having a known mode of action. Wilson et al., teach the profiles provided are indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound. Wilson et al., also identified at least one sequence from the genes which encode the KatG complex that has a level significantly different from bacterial cells not in the presence of INH (page 12,837). Wilson et al., teach the results show that the characteristic drug response is the result of intracellular conditions associated with the drugs mode of action (page 12,838). Wilson et al., teach it is possible to predict the mode of action of a novel compound based on a physiologically derived interpretation of its expression response to that compound (page 12,838). Wilson et al., teach the plurality of sequences equals about 75% or less of the genome of *Bacillus subtilis* cells. However, Wilson et al., do not teach culturing cells of *Bacillus subtilis*.

Cao et al., teach culturing *B. subtilis* strains for DNA microarray analysis (page 1274, col. 2). Cao et al., teach detecting hybridization complexes formed by contacting at least one nucleic acid sample, obtained by culturing *Bacillus subtilis* cells in the presence of at least one subinhibitory amount of an antimicrobial compound having an unknown mode of action, with a plurality of nucleic acid sequence corresponding to

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genes of the *Bacillus subtilis* cells, wherein the plurality of nucleic acid sequences is contained on a substrate (page 1274, col. 2). Cao et al., teach RNA isolation, cDNA synthesis, slide hybridization and labeling (page 1274, col. 2). Cao et al., teach detecting and quantifying the presence, absence or change in the amount of the hybridization complexes, and comparing with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode action, is indicative of the similarity of the mode of actions of the antimicrobial compound and the standard compound using data analysis software (page 1274, col.2).Cao et al., teach northern blot analysis (Figure 2). Cao et al., teach the induction of many genes (page 1271, col.1). Cao et al., teach comparing *M. tuberculosis* to various antibiotics (page 1273, col.1). Cao et al., teach that *B. subtilis* co-exists with many microorganisms and that *Bacillus'* antibiotic resistance genes need control (page 1267, col.2).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the *Bacillus subtilis* strain of Cao et al., to Wilson et al., method for determining the mode of action of an antimicrobial compound in order to provide obtain antimicrobial mode of action results for *B. subtilis* which is known to be resistant to known antimicrobial drugs. One of ordinary skill in the art would have a reasonable expectation of success by exchanging one gram-positive bacterium for another gram-positive bacteria because both bacteria are known in the art to have analyzed on DNA microarrays wherein the hybridization complexes detected in the presence of

antimicrobial compounds. Furthermore, no more than routine skill would have been required to exchange the *M. tuberculosis* of Wilson et al., for the *B. subtilis* of Cao et al., since the ability for pathway characterization is available because complete genome sequences of *B. subtilis* is known along with microarrays containing representatives of each of the gene.

Response to Arguments

4. Applicants' argument filed February 5, 2008 has been fully considered but the argument is not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been prima facie obvious to combine the invention of Wilson et al., and Cao et al., to advantageously achieve a determining drug-induced alterations in gene expression by microarray hybridization for multi-drug resistant bacteria.

Applicants' assert that neither Wilson et al., nor Cao et al., teach the use of sub-inhibitory concentrations however, no more than routine skill is involved in adjusting the concentration of the claimed process to suit a particular starting material in order to

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achieve the results taught in the prior art. Furthermore, optimization within prior art conditions or through routine experimentation is not patentable. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 (“The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”).

Therefore Applicants’ argument is not persuasive and the rejection is maintained.

Conclusion

5. No claims allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645